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EXAMINER	
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ART UNIT	PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)
	09/500,747	GOKHALE ET AL.
	Examiner	Art Unit
	Kathleen M Kerr	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 24 October 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 23,25,26 and 28-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 23,25,26 and 28-39 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,11.

4) Interview Summary (PTO-413) Paper No(s). _____

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____

DETAILED ACTION

Application Status

1. In response to the previous Office action, a first Office action on the merits (Paper No. 14, mailed on February 12, 2002), Applicants filed an amendment and response received on August 16, 2002 (Paper No. 18). Applicants also filed a supplemental response on October 24, 2002 (Paper No. 19). Paper No. 14 amended the specification and Claims 23, 25-26, and 28-39 and canceled Claims 24 and 40-44. Thus, Claims 23, 25-26, and 28-39 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/119,363 filed on February 9, 1999 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

3. A copy of Bohm *et al.*, as cited in the information disclosure statement filed on March 21, 2001 (Paper No. 5), has been filed by Applicants. This reference has been initialed on Paper No. 5; a copy is attached hereto.

4. Other Documents 16-23, as cited in the information disclosure statement filed on May 9, 2000 (Paper No. 11) have been filed by Applicants. These references have been initialed on Paper No. 11; a copy is attached hereto.

Drawings

5. As previously noted, new Figure 3 is considered informal for the reasons detailed in the PTO Form 948. Said form is attached hereto. If said form is not attached, Applicants should telephone the Examiner to receive a faxed copy. Appropriate correction to Figure 3 is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Compliance with the Sequence Rules

6. By virtue of the paper copy filed on September 20, 2001, the instant application fully complies with the sequence rules.

Withdrawn - Objections to the Specification

7. Previous objection to the specification for being incomplete on page 15 is withdrawn by virtue of Applicants' amendment. The Examiner notes that the SEQ ID NOs previously inserting into this paragraph were omitted in this latest amendment. The Examiner has added the SEQ ID NOs; no action is required by Applicants except to change their own copy of the application.

8. Previous objection to the Abstract is withdrawn by virtue of Applicants' amendment.

9. While the Examiner maintains that the clarity of the instant specification would be greatly improved by a drawings, as previously suggested, depicting the general structures of various modular PKSs, the Examiner withdraws the previous objection to the specification requiring such a drawing since the information, as noted by Applicants, is publicly available.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

10. Previous rejection of Claims 24 and 27 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' cancellation of said claims.
11. Previous rejection of Claims 23-39 under 35 U.S.C. § 112, second paragraph, as being indefinite for, the phrases "a C-terminus" and "an N-terminus" (emphasis added) is withdrawn by virtue of Applicants' amendment.
12. Previous rejection of Claims 28-39 under 35 U.S.C. § 112, second paragraph, as being indefinite for the span of modules noted is withdrawn by virtue of Applicants' amendment.
13. Previous rejection of Claims 28-39 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to indicate the use of loading modules is withdrawn by virtue of the Examiner's reconsideration in view of Applicants' arguments.
14. Previous rejection of Claims 24 and 27 under 35 U.S.C. 112, first paragraph, written description, is withdrawn by virtue of Applicants' cancellation of said claims.
15. Previous rejection of Claims 28-39 under 35 U.S.C. 112, first paragraph, written description, is withdrawn by virtue of the Examiner's reconsideration. The withdrawal of the rejection is based on the fact that the art of polyketide synthases has developed to such an extent, with numerous examples of strikingly similar structure and function, that one of skill in the art, while not being able to predict the exact structure (sequence) of a particular PKS, does have enough general knowledge of PKS structure and function to utilize PKS enzymes as a generic genus.

16. Previous rejection of Claims 23-26 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for hybrid PKSs that facilitate transfer from a first module to a second module, does not reasonably provide enablement for hybrid PKSs that do not facilitate transfer from a first module to a second module, is withdrawn by virtue of Applicants' amendment requiring the facilitation of polyketide chain transfer in the claims.

17. Previous rejection of Claims 23-39 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for functional hybrid PKSs using RALs and/or ERLs from the DEBS PKS, does not reasonably provide enablement for functional hybrid PKSs using RALs and/or ERLs from other PKSs is withdrawn by virtue of Applicants' arguments concerning the predictability, use of controls, and Tang *et al.*

Maintained - Claim Rejections - 35 U.S.C. § 112

18. Previous rejection of Claims 23, 25, 26, and 28-39 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms **intra-molecular linkers (RAL)** and **inter-molecule linkers (ERL)** is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the RAL and ERL products are not defined by their own structure, but are defined by the structure of the abutting sequences (the catalytic domains on either end). This argument is not found persuasive because, as noted previously, the "gaps" between defined catalytic regions of PKSs in the art are not large enough to accommodate the RAL and ERL structures. In other words, the RAL and ERL sequences (as described by SEQ ID NOs in Claims 25 and 26) must be carved away from the art-defined endpoints of the catalytic

domains. The instant specification does not provide adequate clarity for defining the metes and bounds of these structures, RAL and ERL.

The Examiner notes that Claim 25 adequately clarifies the RAL used in the claims; however, the ERL remains unclear. Claim 26 does not adequately clarify the ERL used in the claims because the complete structure is not used.

The previous rejection is iterated below:

“Claims 23-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the intervening sequences that Applicants name **intra-molecular linkers (RAL)** and the N-terminal sequences that Applicants name **inter-molecule linkers (ERL)** are unclear.

From the specification (page 9 and Figure 3), the only consensus residue in a 16-20-residue RAL appears to be a *single* proline. The consensus sequence of an N-terminal ERL contains very vague and broad homologies over 32-40 amino acids (double a RAL) based on acidity and basicity of residues without particular definition of the location of these residues. Thus, using these homologies alone, one of skill in the art could not define the metes and bounds of the claimed RALs and ERLs. Additionally, in art-defined PKS sequences, the modules noted do not leave these large gaps (to fit in a RAL, for example) between modules. For example, in GenBank Accession Number M63676 defining the first open reading frame of the DEBS PKS (modules 1 and 2 – in between which should be a RAL as defined by Applicants), base pairs 744-6659 describe the “approximate span of module 1” and base pairs 6678-11219 describe the “approximate span of module 2”; these descriptions leave only 18 (=6678-6659) intervening base pairs which are equivalent to 6 amino acids, not 16-20 residues of a RAL. It is wholly unclear where the extra amino acids for the RAL come from.

In Claims 25 and 26, are these sequences intended to be those as exactly found in Figure 3? If so, these names should be replaced with the appropriate SEQ ID NOS as described in Figure 3. If not, particularly M2rif, M5rif, and M3rap are confusing since these modules have other modules covalently bound on their N and C terminal sides (they are one of at least three modules in an open reading frame, and they are in the middle), and it is unclear which side the RAL is found on.”

19. Previous rejection of Claims 23, 25, 26, and 28-39 under 35 U.S.C. 112, first paragraph, written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the claims are not drawn to RAL or ERL sequences as such, but are drawn to hybrid PKSs in their entirety. While this is true, the adequate description of all individual components in the claimed hybrid PKS is required. In the absence of any defined structure (once removed from its position in a naturally-occurring PKS cluster), this portion of the hybrid construct is claimed only by function. As previously noted, not enough characteristics identifying the claimed genus have been described such that one of skill in the art could predict the structure of other members of the genus.

The previous rejection is iterated below:

"Claims 23-39 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to hybrid PKSs that contain RAL or ERL portions from *any* PKS.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification describes RALs and ERLs as found in the *ery* PKS, the *rif* PKS, and the *rap* PKS (see Figure 3). The structure/function relationship described on page 9 and in Figure 3 do not describe sufficiently identifying characteristics of these claimed RALs and ERLs to support claims to the entire genus of molecules. See also the discussion above concerning the confusing nature of the definition of RALs and ERLs. Thus, the instant claims lack adequate written description."

Withdrawn - Claim Rejections - 35 U.S.C. § 102

20. Previous rejection of Claims 23, 25, 26, and 27 under 35 U.S.C. § 102(b) as being anticipated by McDaniel *et al.* is withdrawn by virtue of the Examiner's reconsideration of the claim language. Clearly in the preamble, the term "hybrid" indicates that some portion of the claimed PKS should be from a different source than the rest of the PKS, not just swapping within the same PKS as taught by the art. Because this art does not teach an appreciation of the linking regions between modules, no motivation to combine this art with other prior art to obviate the claimed invention can be found in the prior art.

21. Previous rejection of Claims 23, 25, 26, and 27 under 35 U.S.C. § 102(a) as being anticipated by Ranganathan *et al.* is withdrawn because the instant claims are granted priority back to the provisional filing date rendering Ranganathan *et al.* not prior art.

NEW ISSUES

Claim Objections

22. Claims 28-39 are objected to because the word "polyketide" preceding the abbreviation "PKS" is redundant since the term ---polyketide--- is interpreted from the ---P--- in PKS. The Examiner suggests deleting the word "polyketide" from the preamble in each case.

Summary of Pending Issues

23. The following is a summary of the issues pending in the instant application. Each issue must be addressed in a complete response to the instant Office action.

a) Figure 3 is informal.

- b) Claims 28-39 are objected to for redundancy in the claims.
- c) Claims 23, 25, 26, and 28-39 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms intra-molecular linkers (RAL) and inter-molecule linkers (ERL).
- d) Claims 23, 25, 26, and 28-39 stand rejected under 35 U.S.C. 112, first paragraph, written description.

Conclusion

24. Claims 23, 25, 26, and 28-39 are rejected for the reasons noted above. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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KMK
October 26, 2002